Starting with Reichstein's substance L acetate, now readily available, a convenient partial synthesis of Reichstein's substance P 21-monoacetate (XVII) and 3,21-diacetate (XVIII) is described. The former was carried through the same transformations as performed in the corresponding 21-desoxy series and afforded two new analogs (XII and XIV) of the important cortical hormone 17α-hydroxy-11-desoxycorticosterone (Reichstein's substance S).

Several of these substances are being subjected to a variety of biological tests particularly in regard to their potential usefulness as antiarthritic agents.

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MEXICO CITY, D. F.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

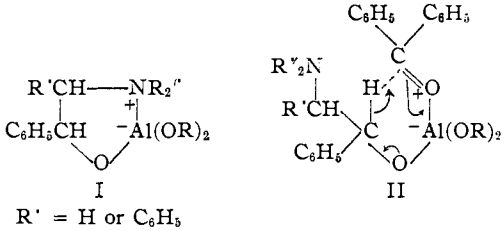
Factors Interfering with the Oppenauer Oxidation of Amino Alcohols[1]

BY ROBERT E. LUTZ, ROBERT H. JORDAN,[2a] AND WILLIAM L. TRUETT[2b,c]

In recent attempts[3] we found that, like quinine,[4a] several typical aliphatic 1,2-amino alcohols did not undergo the Oppenauer oxidation with aluminum *t*-butoxide and benzophenone or cyclohexanone. However, aluminum isopropoxide reductions of the corresponding, and other, α-amino ketones have proceeded without difficulty in all cases tried except the α-(N-alkyl-ethanolamino)-ketones which are cyclic.[5] It follows that under the oxidizing conditions the equilibria[6] lie well over on the side of the reductants.

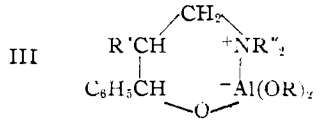
The explanation offered for this phenomenon, involving acid–base combination between nitrogen and aluminum,[4] did not seem to us to explain adequately why the alcoholic group, which would still be free, did not undergo the oxidation with reasonable speed when the solubility of the complex was appreciable, and it did not seem to be consistent with the facility of aluminum isopropoxide reductions of α-amino ketones where presumably similar complexes might be formed.

The phenomena may be explained in terms of stable cyclic complexes of the type (I) which if formed would cause displacement of the equilibrium sharply in favor of the amino alcohol, and which would be expected to interfere seriously with hydrogen transfer if the reaction were an intramolecular one involving a quasi-ring intermediate or transition state such as II.[4,7] Five-membered



I R' = H or C_6H_5 II

ring complexes (I) might well involve a significant degree of added stabilization through second order or "no bond" resonance. Analogous six-membered ring complexes (III) based on 1,3-amino alcohols would be conceivable although resonance stabilization would be excluded or at least greatly diminished because of the break in conjugation involved in the extra methylene group. Larger rings or linear polymeric complexes presumably would not be stable. Thus the amino alcohols might fall



III

into three categories; the 1,2-types which should not undergo the standard Oppenauer oxidation; 1,4 and 1,5 and longer amino alcohols which should generally be oxidizable without difficulty; and the intermediate 1,3-amino alcohols where a less predictable reaction might depend on structural and steric effects. Preliminary studies, successful as far as they have gone, have been made to test these predictions.

Nine typical 1,2-amino alcohols (IVa-c, V, and XIII–XVII of Table I) including one diasteroisomeric pair (IVb and c), were recovered unchanged employing aluminum *t*-butoxide and benzophenone or cyclohexanone; three of these were used in the form of the free bases, four as the hydrochlo-

(1) The work of this paper was supported in part by a grant-in-aid from the National Institutes of Health, recommended by the National Cancer Institute, and it stemmed from the program of syntheses of 1,2-amino alcohols as tumor-necrotizing agents.

(2) (a) Post-doctorate Fellow; (b) Philip Frances du Pont Fellow; (c) assisted by Preston H. Leake and Rosser L. Wayland, Jr.

(3) The first unsuccessful Oppenauer oxidations in this laboratory were carried out by Dr. R. S. Murphey using aluminum isopropoxide. Mr. C. R. Bauer then used aluminum *t*-butoxide on IVa which will be described in a later publication.

(4) (a) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945). *Cf.* (b) Doering and Aschner, *ibid.*, **71**, 838 (1949). (c) Doering and Young, *ibid.*, **72**, 631 (1950).

(5) (a) Lutz, Freek and Murphey, *ibid.*, **70**, 2015 (1948); (b) Lutz and Jordan, *ibid.*, **71**, 996 (1949).

(6) Concerning the reversibility of this reaction, *cf.* (a) Wilde, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178; (b) "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, p. 155; (c) Adkins, Elofson, Rossow and Robinson, THIS JOURNAL, **71**, 3622 (1949); (d) Adkins and Cox, *ibid.*, **60**, 1151 (1938); (e) Baker and Adkins, *ibid.*, **62**, 3305 (1940); (f) Baker and Schafer, *ibid.*, **65**, 1675 (1943).

(7) (a) Baker and Linn, *ibid.*, **71**, 1399 (1949); (b) Lutz and Gillespie, *ibid.*, **72**, 344 (1950); (c) Jackman and Mills, *Nature*, **164**, 789 (1949).

rides, and two both as hydrochlorides and as bases. As a check on these findings a reduction in a typical case (XIV·HCl) was carried out, successfully, under conditions similar to those employed in the Oppenauer oxidations using toluene, with aluminum *t*-butoxide and benzhydrol in place of aluminum isopropoxide and isopropyl alcohol. The equilibria in the presence of excess aluminum *t*-butoxide are thus shown to be consistently far over on the side of the amino alcohols.

$$\begin{array}{c} C_6H_5CH{-}CHC_6H_5 \\ | \quad\quad | \\ OH \quad NR_2 \end{array}$$

IV

NR_2 = (a) $N(C_2H_5)CH_2CH_2OCH_3$[3]; (b) NC_5H_{10}(isomer-A); (c) isomer-B; (d) NHC_6H_5; (e) $N(CH_3)C_6H_5$

$$\begin{array}{c} C_6H_5CHCH_2NC_5H_{10} \\ | \\ OH \end{array}$$

V

(NC_5H_{10} = piperidyl)

It is noteworthy that no stereochemical equilibration of the epimeric amino alcohols (IVb and c) occurred in the attempted Oppenauer oxidations using aluminum *t*-butoxide, a fact which in itself indicates that the oxidation rate is exceedingly low.[4b]

The 1,2-anilino alcohols are of interest because of their comparatively weakly basic nitrogen. In two cases (IVd and e) the Oppenauer oxidation under the usual conditions gave mixtures seemingly the result of partial reaction; in the case of IVd a small amount of the pure α-anilino ketone (XXI) was isolated and identified; and in the case of IVe some pure unchanged material was finally isolated from the mixture and identified. Thus it appears that N-aryl α-amino nitrogen is not as effective as aliphatic alkylamino nitrogen in interfering with the oxidation.

In three cases chosen arbitrarily (IVb, IVc and V), under comparable conditions, successful oxidations of 1,2-amino alcohols to the amino ketones were accomplished using an excess of potassium *t*-butoxide. In one of these cases (IVb) a catalytic amount of potassium *t*-butoxide was used, with similar results at the higher temperature necessary to achieve reaction within a reasonable time; this experiment showed that the oxidation had not proceeded by virtue of stabilization of the amino ketone in the form of an addition compound or an enolate. It therefore follows that the true 1,2-amino ketone–amino alcohol equilibrium is not as far different from the equilibria of simple ketone-alcohol systems as might have been supposed[6c] but is sharply displaced in the direction of the amino alcohol by an excess of aluminum *t*-butoxide.

A typical 1,4-amino alcohol (VI) was prepared where chelation is excluded on steric grounds. As was anticipated this compound was readily oxidized to the γ-amino ketone (XX) under the Oppenauer conditions using cyclohexanone and aluminum *t*-butoxide. Other pertinent examples are the successful aluminum phenoxide–cyclohexanone oxidations of the alkaloids yohimbine and corynanthine which are 1,6-amino alcohols.[8,6b] It is concluded therefore that in those cases where the amine nitrogen and alcoholic hydroxyl are separated from each other by a chain of at least four carbons Oppenauer oxidations generally will be successful.

$$C_6H_5CHCH_2CH_2CH_2NC_5H_{10}$$

VI

OH (NC_5H_{10} = piperidyl)

In the case of the intermediate 1,3-type amino alcohols the situation is complicated by the tendency of the β-amino ketones to lose nitrogen.[9] *p*-Chloro and *p*-bromo-β-aminopropiophenones[10c] are extensively deaminated during aluminum isopropoxide reductions. Other amino ketones of this type are deaminated during catalytic reductions.[10a,b]

The reaction between aluminum isopropoxide and 1,2-diphenyl-3-piperidyl-1-propanone (VII) proceeded exceedingly slowly with deamination as the chief result, but catalytic reduction was reasonably successful and gave the amino alcohol (VIII). This amino alcohol either as the free base or as the salt was recovered unchanged (35–43%)

$$\begin{array}{c} C_6H_5COCHCH_2NC_5H_{10} \\ | \\ C_6H_5 \end{array} \xrightarrow{Pt + H_2}$$

VII

(NC_5H_{10} = piperidyl)

$$\begin{array}{c} C_6H_5CH{-}CHCH_2NC_5H_{10} \\ | \quad\quad | \\ OH \quad C_6H_5 \end{array}$$

VIII

after treatment with aluminum *t*-butoxide and cyclohexanone or benzophenone, but it was destroyed using potassium *t*-butoxide as the catalyst. It should be noted that because this amino alcohol is relatively stable under the usual Oppenauer oxidation conditions, it follows that the amino ketone (VII), which is largely albeit slowly deaminated under aluminum alkoxide reduction conditions, has not in this case first undergone reduction; the deamination must have involved the ketone, directly, in a reaction (perhaps initially enolization) which competed successfully with a very slow reduction. It is clear from these experiments that neither aluminum alkoxide oxidation nor reduction goes readily here.

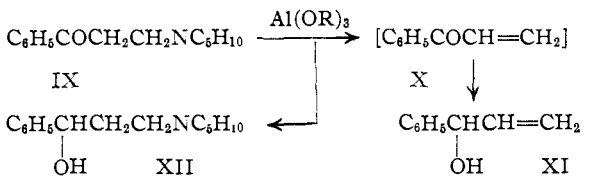
In the case of β-piperidylpropiophenone hydrochloride (IX), in contrast with the *p*-chloro and *p*-bromo analogs[10c] referred to above, aluminum isopropoxide reduction gave a 65% yield of the desired amino alcohol (XII), and a 20% yield of a non-basic product which was identified as phenyl vinyl carbinol (XI). The latter compound was

(8) (a) Janot and Goutarel, *Bull. soc. chim.*, 509 (1949); (b) Witkop, *Ann.*, **554**, 83 (1943).

(9) *Cf.* (a) Mannich and Heilner, *Ber.*, **55**, 363 (1922); (b) Blicke and Burckhalter, THIS JOURNAL, **64**, 451 (1942); (c) Snyder and Brewster, *ibid.*, **70**, 4231 (1948).

(10) *Cf.* (a) May and Mosettig, *J. Org. Chem.*, **11**, 105 (1946); (b) Schultz, *et al.*, *ibid.*, **11**, 314 (1946); (c) Lutz, *et al.*, *ibid.*, **12**, 660 (1947).

presumed to have resulted from deamination of the β-amino ketone to phenyl vinyl ketone (X) and subsequent reduction of the carbonyl group. Incidentally it is interesting to note at this point,



that, as would have been expected, the para substitution of halogen in IX favored the deamination reaction.[10c] The amino alcohol (XII) either in the form of the base or the hydrochloride was converted into non-crystalline non-basic products in an Oppenauer oxidation using aluminum *t*-butoxide. The stability of the amino alcohol and the instability of the amino ketone under the reaction conditions were demonstrated in independent experiments in which the oxidant was omitted. It is therefore inferred that the Oppenauer oxidation took place with appreciable speed in this series, but no inference can be drawn as to the relative position of the oxidation–reduction equilibrium.

Steric hindrance to reaction may be an important or dominant factor in the 1,3-amino alcohol series where there is little or no activation of the carbonyl groups. This might explain the fact that the amino alcohol VIII is not oxidized readily nor is the amino ketone VII readily reduced using aluminum alkoxides under the usual conditions. On the other hand if a six-membered ring complex (III) were possible here, then the differing behaviors of the two compounds VIII and XII might be attributed to an understandable though perhaps not predictable difference in ease of cyclization or stability of the complex (*cf.* the striking effect of N-substitution in facilitating cyclization of α-(ethanolamino)-ketones to hydroxymorpholines).[5]

It is possible that equilibria in all of these reactions may be affected significantly by differences in conditions, solvent and reagent, under which the two opposite reactions are studied. The stabilities and solubilities of the nitrogen–aluminum complexes might well be affected by the basicity of nitrogen which should be greater in the 1,2-amino alcohols than in the α-amino ketones. However, since the oxidations of the 1,4- and longer amino alcohols proceed normally in spite of their presumably still higher basicities[11] and their presumably readier tendency to form simple acid-base complexes, the basicity effects alone would appear to be negligible in this connection.

An alternative to the ring-complex explanation of the interference with the Oppenauer oxidation of 1,2-amino alcohols may be suggested in terms of the effect of resonance involved in the conjugation of the C—O or C=O groups with the C—N linkage (inductive effect). The 2-nitrogen should increase the activity of the carbonyl group toward aluminum alkoxide reduction and at the same time diminish the oxidizability of the carbinol α-hydrogen. These influences would operate in the 1,3- and longer amino alcohol and ketone systems with progressively diminishing intensities, and perhaps effectively only when coupled with appreciable steric effects (*e. g.*, VIII). This alternate hypothesis however does not explain the shift of the equilibrium toward the amino ketone in a typical case in the 1,2- types (IVb) when a catalytic amount of potassium *t*-butoxide was used.

In a recent paper by Adkins, *et al.*,[6c] on "oxidation potentials" of a series of ketones, calculated from equilibria, it is reported that α-(N-piperidyl)-acetophenone has an oxidation potential higher by 85 mv. than that of acetophenone itself, but that the equilibration rate is considerably lower. Unfortunately equimolar or slightly larger amounts rather than catalytic amounts of aluminum *t*-butoxide were used in the equilibrations.[6c] The observed and very low equilibration (*i. e.*, oxidation) rate would be an expected consequence of the formation of a stable amino alcohol complex such as I. It is doubtful that catalytic amounts of aluminum *t*-butoxide would have been adequate. However, catalytic amounts of potassium *t*-butoxide probably could have been used successfully (as here in the case of IVb) because of the absence of impeding complex formation and because of the high hydride–α-hydrogen activity in, and greater concentration of, the alkoxide ions produced by exchange with *t*-butoxide ions; and this might have led to results more nearly representative of the true amino ketone–amino alcohol oxidation–reduction system.

The ideas discussed above suggested other problems of interest in this field, *e. g.*, the effect of an adjacent hydroxyl, alkoxyl or carbonyl on the Oppenauer oxidation. Allopregnane-3,17,20-triol, which is a typical example, is only partially oxidized by aluminum phenoxide–acetone–benzene to the 3-keto compound,[12] possibly because of protection of the 17 and 20-hydroxyls in the form of a five-membered phenoxyaluminum glycolate ring. The sharp raising of "oxidation potentials" of ketones by alpha[6c] or *ortho*[6f]-methoxyl groups might be explained in part on the basis of chelate complexes analogous to I.

Experiments are in progress to put the idea of cyclic complexes to other tests. If the idea is correct then the *trans*-cyclopropane, cyclobutane, and other related 1,2-amino alcohols, should undergo the Oppenauer oxidation, whereas the *cis* isomers should not (and incidentally this reaction should offer a dependable means of determining configurations in such types). On the other hand, should the *cis* and *trans* isomers both fail to undergo the Oppenauer oxidation, it would

(11) The basicities of two typical 1,2-amino alcohols are significantly lower than those of the corresponding phenethylamines (Spencer, Leffler and Burger, unpublished results).

then be clear that ring complexes are not involved. A similar study of some *cis* and *trans* cyclic 1,2-glycols and glycol monoalkyl ethers is also projected in this connection.

Acknowledgment.—Extensive contributions to the experimental work were made by Preston H. Leake and Rosser L. Wayland, Jr.

Experimental[12]

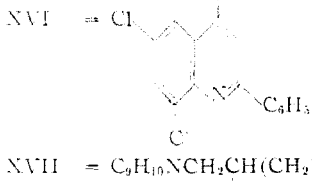
Aluminum and potassium *t*-butoxide oxidations, summarized in Table I, were carried out according to the following general procedures: The reaction mixture consisted of 0.01 mole of the compound in the form of the base or the hydrochloride, 150 ml. of solvent, dry toluene [or

TABLE I

OPPENAUER OXIDATIONS

Compound	Procedure	Product	Yield, %
IVb	B, G, L	IVb	40
IVb·HCl	B, G, L	IVb	46
IVb	A,[a] C, F,[b] L	XVIII	66[c]
IVb·HCl	A, C, F, G	XVIII	18
IVc	B, G, L	IVc	61
IVc	D, I, L	IVc	79
IVc·HCl	B, G, L	IVc	54
IVc	A, C, F, G, L	XVIII	32
XVIII·HCl	B, G, L	XVIII	50
IVd	C, H, I, N	XXI	10
IVe	C, G, L, O	...	...
V	B, G, M	V	60
V	A, C, F, G, M	XIX	35
VI	B, G, M	XX	82
XII	B, G, L	IX or XII[d]	0
XII·HCl	B, G, L	IX or XII[d]	0
XII·HCl	E, G, L	XII	44
IX·HCl	B, G, M	IX[e]	0
VIII	B, G, L	VIII	40
VIII	A, C, G, L	VIII	35
VIII·HCl	A, C, G, L	VIII	43
VIII	A, E, F, G, L	VIII	62
VIII	A, C, F, G, L	VII or VIII[e]	0
VII	A, C, G, L	VII	34
VII	A, C, F, G, L	VII[e]	0
XIII	D, G, K	XIII	70
XIII	D, I, K	XIII	54
XIV·HCl	D, G, M	XIV·HCl	28
XV·HCl	D, I, M	XV·HCl	76
XVI·HCl	D, I, J	XVI·HCl	71
XVII	D, I, K	XVII	92
XXII·HCl	G,[f] M	XIV·HCl	13

[a] The benzene evaporated during the experiment and the reaction mixture stood at *ca.* 150° for over ten hours. In another experiment using xylene as the medium and refluxing for 20 hours a 45% yield of crude XVIII–HCl was obtained, purified (16%) and identified. [b] A quarter of an equivalent of potassium *t*-butoxide (0.0025 mole) was used. [c] Crude but nearly pure. [d] This run, in toluene as the solvent, using 0.3 mole of benzhydrol rather than benzophenone, and refluxing for three hours, resulted in recovery of unchanged material, but under refluxing for twenty-one hours gave the amino alcohol XIV·HCl in 13% yield (purified). It should be noted that there was considerable resinification in this experiment. [e] These compounds were specifically sought among the products but were not found.

XIII = 4-BrC$_6$H$_4$CHOHCH$_2$NC$_4$H$_8$O(morpholinyl)
XIV = 4-IC$_6$H$_4$CHOHCH$_2$N(*n*-butyl)$_2$
XV = 3-Cl,4-CH$_3$C$_6$H$_3$CHOHCH$_2$N(CH$_3$)CH$_2$C$_6$H$_5$
XVI = 
XVII = C$_9$H$_{10}$NCH$_2$CH(CH$_2$)$_8$CHCH$_2$NC$_9$H$_{10}$ (OH, OH)
(C$_9$H$_{10}$ is tetrahydroisoquinolyl)
XVIII = C$_6$H$_5$COCH(C$_6$H$_5$)NC$_5$H$_{10}$
XIX = C$_6$H$_5$COCH$_2$NC$_5$H$_{10}$
XX = C$_6$H$_5$COCH$_2$CH$_2$CH$_2$NC$_5$H$_{10}$
XXI = C$_6$H$_5$COCH(C$_6$H$_5$)NHC$_6$H$_5$
XXII = C$_6$H$_5$COCH(C$_6$H$_5$)N(CH$_3$)C$_6$H$_5$
XXIII = 4-IC$_6$H$_4$COCH$_2$N(*n*-butyl)$_2$

A) dry benzene], oxidant, (B) 0.4 mole of cyclohexanone, or (C) 0.05 mole or (D) 0.1 mole of benzophenone, [or (E) no oxidant at all but with 0.4 mole of added *t*-butanol (for the purpose of testing the effect of reaction conditions)], and 0.03–0.04 mole of aluminum [or in some cases (F) potassium] *t*-butoxide. This mixture was refluxed for (G) 17–20, (H) 24 or (I) 40 hours, poured into ice water, made alkaline with 10% sodium hydroxide to dissolve aluminum hydroxide, and separated, with appropriate extraction by added ether where needed. The combined organic solvent extract was washed and the basic material removed by extractions with portions of 2 *N* hydrochloric acid until test showed the extraction to be completed. [In some cases (J) the combined organic solvent extract was instead dried over sodium sulfate and treated with ethereal hydrogen chloride to precipitate the hydrochloride.] The combined aqueous extract was cooled by addition of ice and the base was precipitated by addition of 10–20% sodium hydroxide, or in a few cases by sodium carbonate. If the product solidified (K) it was filtered and recrystallized from ethanol; otherwise the resulting oil was extracted with ether, and the solution was dried over sodium sulfate and either (L) evaporated under reduced pressure followed by crystallization of the base from ethanol, or (M) the hydrochloride was precipitated by addition of ethereal hydrogen chloride and recrystallized. The products were identified by mixture melting points which in this field seem generally to be reliable even for the salts. In all the experiments listed, except two as indicated, only the one crystalline product indicated was obtained with no indication that the corresponding amino ketone was present as a significant impurity; the yields listed refer to relatively pure material. The rest of the material was accounted for in part through losses in manipulation and in part by the formation of non-crystalline by-products. (N) In the case of IVd, the product (hydrochlorides) was converted to the bases. It was evidently a mixture of the amino alcohol and amino ketone. Fractional crystallization from ethanol gave a small amount of pure amino ketone (XXI) which was identified by mixture melting points. (O) The product in the case of IVe was evidently a mixture. Fractional crystallization gave a small yield of unchanged amino alcohol which was identified by mixture melting point.

N-Desylaniline (XXI) was made in 35% yield by the Voigt reaction[13] from benzoin, aniline and phosphorus pentoxide under heating for four hours at 100°. Reduction of 14.3 g. with 30 g. of aluminum isopropoxide in 200 ml. of isopropyl alcohol under reflux for three hours, evaporation under reduced pressure, hydrolysis in ice and extraction with ether, gave a crystalline residue (IVd)

(12) Microanalyses by Mrs. Anne Wilgus and Clark Microanalytical Laboratory.

(13) (a) Voigt, *J. prakt. Chem.*, **34**, 1 (1886); (b) also ref. 5a.

which was recrystallized from ethanol; 12 g. (84%); m. p. 122–124° (Voigt,[14a] 119°).

N-Desyl-N-methylaniline (XXII) was made by condensation of 23 g. of desyl chloride and 35 ml. of methylaniline (100° for four hours), and crystallized from ethanol; pale yellow; yield 12 g. (40%); m. p. 99.5–101.5°.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35. Found: C, 83.74; H, 6.51.

1,2-Diphenyl-2-(N-methylanilino)-ethanol (IVe).—Reduction of 12 g. of XXII by aluminum isopropoxide (as above) and crystallization of the product from ethanol gave 4.2 g. (34%); m. p. 110.5–112°.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98. Found: C, 83.18; H, 6.58.

α-(Piperidylmethyl)-benzyl Alcohol (V).—Reduction of 5 g. of XIX[14] (see Table I) with 45 ml. of 1.8 *N* aluminum isopropoxide under slow distillation for three hours, and recovery of material by hydrolysis in dilute sodium hydroxide, extraction with ether, precipitation of the salt by ethereal hydrogen chloride, liberation of the base by dilute sodium carbonate and extraction by ether, gave 3 g. of crystals of m. p. 67–68° (60%) (B. and B.,[15] 69–70°). Preparation from styrene bromohydrin in refluxing benzene (48 hours); yield 36%. The **hydrochloride** was crystallized from alcohol by addition of ether; m. p. 192–194° (B. and B.,[14] 193–194°).

Anal. Calcd. for $C_{13}H_{19}NO{\cdot}HCl$: C, 65.13; H, 7.57. Found: C, 65.21; H, 7.45.

α-Piperidylacetophenone hydrochloride[15] (XIX, Table I), when recovered in the several experiments, was identified by mixture melting point with material prepared from phenacyl bromide and piperidine. We found the melting point to be somewhat higher than reported[15]; it began to soften at 210° and melted over 228–230° (initial bath temperature 200° and heating rate 1° per minute).

1,2-Diphenyl-3-piperidylpropanol-1 (VIII).—The amino ketone[14,15] (VII) (12 g.) in ethanol, acidified with 5 ml. of concd. hydrochloric acid beyond that necessary to give the congo reaction, was reduced[16] with platinum and hydrogen at 3 atmospheres (1.5 hours); the theoretical amount of hydrogen was absorbed. The crystalline precipitate which had appeared was dissolved by heating, and the solution was filtered and cooled; yield 6.4 g. (53%); m. p. 254–256°.

Anal. Calcd. for $C_{20}H_{25}NO{\cdot}HCl$: C, 72.38; H, 7.90. Found: C, 72.36; H, 8.21.

The **base (VIII)** was liberated by sodium carbonate and crystallized from isoöctane; m. p. 91–93°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. Found: C, 81.47; H, 8.22.

Reaction of the amino ketone (VII) with aluminum isopropoxide proceeded only very slowly. Precipitation of a complex from which VII could be recovered on hydrolysis, occurred quickly; this changed slowly upon long heating (eight hours) into a complex which dissolved completely in aqueous sodium hydroxide. No basic product was precipitated, and it appeared that deamination was the chief result.

β-Piperidylpropiophenone (IX) hydrochloride was reduced[15,16] in ethanol with platinum and hydrogen at 3 atmospheres with absorption of the calculated amount in 35 minutes. The product (XII hydrochloride) crystallized upon addition of ether to the filtered solution; yield 67%. Aluminum isopropoxide reduction[10] of 20 g. of IX with 50 g. of reagent in 300 ml. of isopropyl alcohol under reflux for six hours, followed by hydrolysis in ice and hydrochloric acid, and extraction with ether, gave an oil [2 g. (20%), collected at 70–90° (5 mm.); $n^{22.5}D$ 1.520] which was identified as (XI)[17] by conversion into tri-

(14) Blicke and Blake, THIS JOURNAL, **52**, 235 (1930).

(15) Mannich and Lammerling, *Ber.*, **55**, 3524 (1922).

(16) *Cf.* reduction of β-piperidylbenzylacetophenone: J. D. Smith, Doctorate Dissertation, University of Virginia (1946).

(17) (a) Klages and Klenk, *Ber.*, **39**, 2554 (1906); (b) Meisenheimer and Link, *Ann.*, **479**, 245 (1930).

brompheuylpropane[18a] and the *p*-nitrobenzoate[18b] (identified by m. p. 123–124° and 46–48°, respectively). The acid solution of the amino alcohol (XII) was treated with excess dilute sodium hydroxide and chilled, and the precipitated solid base was filtered and recrystallized from petroleum ether; m. p. 63–64°; yield 11.3 g. (65%). In one experiment the base was distilled; b. p. 170° (50 mm.). It gave no mixture melting point depression with the sample prepared by catalytic reduction (above).

4-Piperidyl-1-phenylbutanol-1 (VI) made by the method of Marxer,[18a] was obtained under difficulties similar to those experienced by Hauser[17a] in analogous syntheses. The *hydrochloride* crystallized from ethanol by addition of ether, and melted at 127.5–128.5° (Marxer[18a] reported 109–111°). It contained persistent water of crystallization which was eliminated upon drying in a desiccator over ascarite for several days.

Anal. Calcd. for $C_{15}H_{23}NO{\cdot}HCl$: C, 66.67; H, 8.99. Found: C, 66.77; H, 9.01.

The *base* was an oil,[18a] b. p. 152–153° (0.5 mm.); $n^{25}D$ 1.5297.

Anal. Calcd. for $C_{15}H_{23}NO{\cdot}HCl$: C, 77.20; H, 9.93; N, 6.00. Found: C, 77.36; H, 10.08; N, 6.28.

It crystallized as the *monohydrate* when exposed to the atmosphere; recrystallization from *n*-hexane gave photosensitive crystals; m. p. 53–54°. It lost its solvent of crystallization and reverted to an oil on standing over calcium chloride in a desiccator.

Anal. Calcd. for $C_{14}H_{23}NO{\cdot}H_2O$: C, 71.67; H, 10.02. Found: C, 71.94; H, 10.38.

γ-Piperidylbutyrophenone (XX of Table I) was extracted by 4 *N* hydrochloric acid in the usual way (above) but it partially crystallized from this solution; the material was filtered at this point and combined with the rest of the product which was subsequently isolated in the usual way (see M above). It was recrystallized from ethyl acetate by addition of ether; m. p. 185–186°. Drying at 60° *in vacuo* was necessary to remove water of crystallization which was partially regained with great rapidity upon exposure to the atmosphere.

Anal. Calcd. for $C_{15}H_{21}NO{\cdot}HCl$: C, 67.20; H, 8.28. Found: C, 66.90; H, 8.06.

Summary

Nine typical 1,2-amino alcohols failed to undergo the Oppenauer oxidation under the usual conditions using aluminum *t*-butoxide; but three were successfully oxidized using potassium *t*-butoxide. Two 1,2-anilino alcohols seemed to be partially oxidized under the usual Oppenauer conditions. One 1,3-amino alcohol failed to undergo the Oppenauer reaction, but another apparently did react. A typical 1,4-amino alcohol was oxidized under the usual Oppenauer conditions without difficulty.

The deamination product obtained in the attempted aluminum isopropoxide reduction of β-piperidylpropiophenone was identified as phenylvinylcarbinol.

Explanation of the interference with the Oppenauer oxidation of aliphatic 1,2-amino alcohols is offered in terms of five-membered chelate complexes involving aluminum, the alcoholic hydroxyl and amine nitrogen.

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(18) (a) Marxer, *Helv. Chim. Acta*, **24**, 222E (1941); (b) *cf.* also Breslow, Walker, Yost and Hauser, THIS JOURNAL, **67**, 1472 (1945).